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Severe Form of Freeman-Sheldon Syndrome Associated With Brain Anomalies and Hearing Loss

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We describe a child with whistling face and multiple contractures, including ulnar deviation of fingers, compatible with a diagnosis of Freeman-Sheldon syndrome (FSS). This patient also presented severe hypertonicity, multiple episodes of pneumonia, difficulty in swallowing, and poor weight gain, which are characteristic of the most severe cases of FSS.

A brain CT scan showed cerebellar and brainstem atrophy. Auditory brainstem responses were absent. The child died at 5 months of respiratory failure.

This case suggests the possibility that, especially in the most severe forms, brain abnormalities may be responsible for some of the clinical manifestations of this syndrome, i.e., respiratory problems, difficulty in swallowing and severe hypertonicity. We assume that there is more than one pathogenetic mechanism (muscular, skeletal, and neurological) underlying FSS, which, together with the genetic heterogeneity and the wide range of clinical symptoms leads us to suggest that it is more appropriate to speak of a Freeman-Sheldon spectrum rather than syndrome and that thorough investigation for CNS and auditory abnormalities should be part of the initial work-up of these patients. © 1996 Wiley-Liss, Inc.

KEY WORDS: **Freeman-Sheldon syndrome, cranio-carpo-tarsal dysplasia, whistling face syndrome, brain defect, hearing loss**

INTRODUCTION

Freeman-Sheldon syndrome (FSS) is characterized by a whistling face with long philtrum, puckered mouth, microstomia, H-shaped cutaneous dimpling on the chin, multiple joint contractures with camptodactyly, ulnar deviation of fingers, windmill vane hand, bilateral talipes equinovarus, and kyphoscoliosis [Burian, 1963; Weinstein and Gorlin, 1969; O'Connell and Hall, 1977]. Clinical severity and phenotypic abnormalities can be variable: hands may be normal and the typical whistling face is reported in only about 50% of patients [Walbaum et al., 1973; Antley et al., 1975; O'Connell and Hall, 1977; Wettstein et al., 1980].

FSS has been classified among the congenital multiple myopathic arthrogryposis based on the possible myopathic origin of both facial anomalies and joint contractures [Vanek et al., 1986]. This syndrome presents genetic heterogeneity [Fitzsimmonds et al., 1984; Wang and Lin, 1987]. There are reports of both autosomal dominant [Fraser et al., 1970; Wettstein et al., 1980], and autosomal recessive cases [Alves and Azevedo, 1977; Kousseff et al., 1982; Dallapiccola et al., 1989], which are phenotypically indistinguishable.

The psychomotor development of the affected children is usually normal [Weinstein and Gorlin, 1969; Vanek et al., 1986; Wang and Lin, 1987], although mild motor delays attributed to joint anomalies, have been occasionally reported [Rintala, 1968; Emery and Nelson, 1970; Antley et al., 1975; O'Connell and Hall, 1977; Fitzsimmonds et al., 1984].

The most severe complications described in FSS are the difficulty in swallowing and the pulmonary problems; the former ascribed to the mouth deformity [Weinstein and Gorlin, 1969; Fraser et al., 1970; O'Connell and Hall, 1977; Kousseff et al., 1982] and the latter due to a decreased thoracic expansion [Fraser et al., 1970; MacLeod and Patriquin, 1974; Vanek et al., 1986]. Neither neurologic nor auditory abnormalities have been previously reported.

CLINICAL REPORT

G.M. was a male of Caucasian origin. At birth, his mother was 33 years old, gravida 5, para 3, and his father was 38 years old. Parents are healthy and noncon-

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sanguineous. Their first child was born at term by spontaneous vaginal delivery and died after 24 hours due to respiratory failure. According to the parents, and the attending doctors, this baby had no resemblance to the present case. The second and fourth pregnancies resulted in spontaneous abortions. The family history was unremarkable. Birth weight was 2,400 g, length was 46 cm, OFC was 34.5 cm, and thoracic circumference was 30 cm. He was hypertonic and had moderate respiratory distress at birth.

We saw this patient for the first time at 3 months. He had poor weight gain, possibly related to difficulty in sucking. His weight was 2,360 g (−4 SD), length was 46.5 cm (−6 SD), and OFC was 34.5 cm (−5 SD). He had marked hypertonia with all limbs in a flexed posture.

The face showed hypertelorism, epicanthus, blepharophimosis with dacryocystitis, small nose with narrow nostrils and hypoplasia of alae, long philtrum, microstomia with puckered mouth, reduced opening of the mouth, highly arched palate, mandibular hypoplasia, and apparently low-set ears.

Other abnormalities included mild kyphoscoliosis, multiple joint stiffness, flexion contractures of the fingers with ulnar deviation, camptodactyly, mild hip dysplasia, partial syndactyly of second and third toes, and slight metatarsal adduction, bilateral inguino-scrotal hernia which was larger on the right (Fig. 1).

The clinical course was characterized by respiratory problems due both to difficulty in clearing the upper airways from mucus secretions, and to reduced thorax expansion. Chromosome and muscle enzyme studies were normal.

The auditory brainstem response (ABR) recording evaluation showed a bilateral absence of the evoked potentials at the highest level of stimulation. No other abnormalities except those clinically obvious were detected on a skeletal survey.

A head CT scan showed "atrophy" of medulla oblongata, pons, midbrain, cerebellar hemisphere, and vermis, with dilated surrounding CSF spaces. There were no significant abnormalities of the supratentorial structures (Fig. 2). The patient died at home at 5 months; an autopsy was not performed.

DISCUSSION

The phenotypic manifestations of FSS are well known and recognizable at birth [Jones, 1988; Gorlin et al., 1990]. The pathogenetic mechanism underlying its typical pattern of multiple contractures has not been fully elucidated. Vanek et al. [1986] described this syndrome as a "non-progressive or slowly progressive myopathy characterized by congenital fiber type disproportion with predominantly facial, limb and possibly respiratory muscle involvement." However, in this and other reports, both the EMG and the structural abnormalities were not detected in all of the involved muscles [Sharma and Tandon, 1970; Sauk et al., 1974; Vaitiekaitis et al., 1979; Vanek et al., 1986]. In addition, the most frequently described muscle abnormality, i.e., the substitution of muscle tissue with connective tissue, may be a consequence rather than a cause of joint immobility [Fitzsimmonds et al., 1984]. The original hypothesis of bony alterations underlying the joint blockage, which led to the definition of this syndrome as

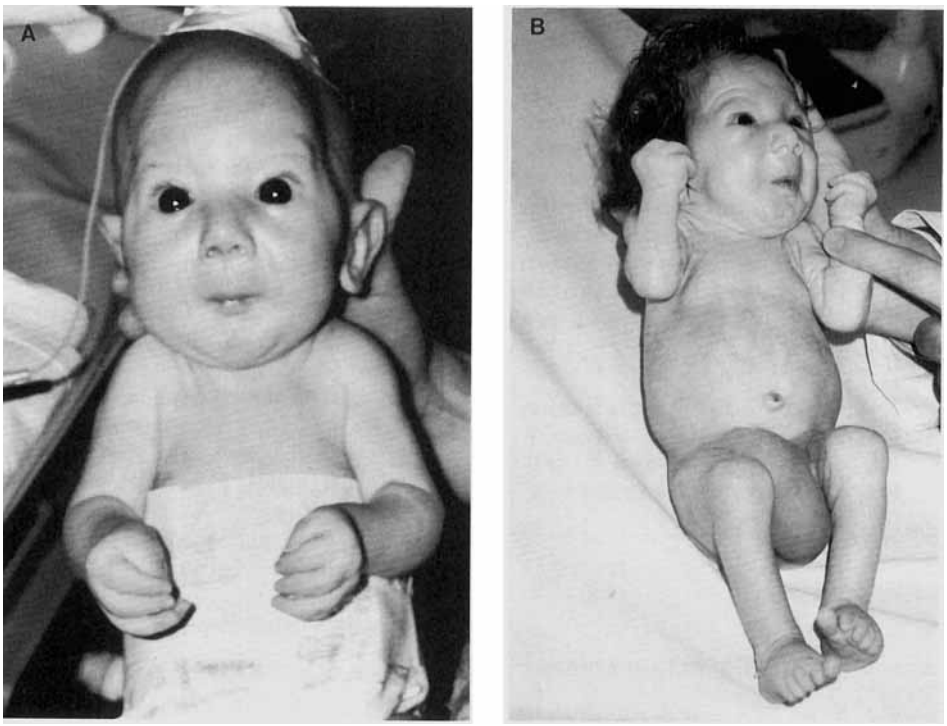

Fig. 1. The patient at 3 months. **A:** Note the hypertelorism, long philtrum, whistling, puckered mouth, short neck; flexion contractures of the finger with ulnar deviation. **B:** Note the inguino-scrotal hernia.

Fig. 2. CT of brain. Atrophic changes of subtentorial structures: cerebellar hemisphere, vermis, and medulla oblongata with dilated surrounding CSF spaces.

cranio-carpo-tarsal dystrophy [Freeman and Sheldon, 1938], is not very convincing. Indeed the bony abnormalities might be a secondary phenomenon consequent to muscular hypertonicity [O'Connell and Hall, 1977].

The possibility that cerebral anomalies may be among the causes of multiple congenital arthrogryposis similar to FSS was forwarded by Illum et al. [1988] and was later confirmed by Schrander-Stumpel et al. [1991], and Di Rocco et al. [1992]. Illum et al. [1988] reported on three children from a sibship of four with a lethal autosomal recessive condition characterized by congenital contractures, including ulnar deviation of fingers, whistling face, and calcifications of the nervous system which have only been detected at autopsy. The clinical course was notable for failure to thrive, difficulty in swallowing and respiratory problems, and one of these patients also had bilateral inguinal hernias. The authors distinguished this condition from FSS on the basis of its severe clinical course. Our patient seems to overlap the Freeman-Sheldon and Illum syndromes. In fact, he presented the typical FSS manifestations as well as brain anomalies and severe clinical course.

The CNS abnormalities documented in this patient are characterized by a pattern of atrophic changes limited to the subtentorial portion of the CNS and are particularly evident in the region of the medulla oblongata. They are quite peculiar and it would be difficult to explain them on the basis of perinatal complications. Brain stem abnormalities could account for the abnormal respiratory, and cough reflex; these in turn may contribute to the respiratory problems described in FSS [Fraser et al., 1970; MacLeod and Patriquin, 1974; Wettstein et al., 1980; Laishley and Roy, 1986; Vanek et al., 1986]. CNS abnormalities may also be involved in the severe hypertonicity observed in these patients.

If CNS abnormalities are responsible for some of the clinical manifestations of this condition, we can assume that there is more than one mechanism (muscular, skeletal, and neurological) involved into the pathogenesis of the FSS.

The different pathogenesis together with genetic heterogeneity and the wide range of clinical symptoms lead us to suggest that it is more appropriate to speak of a Freeman-Sheldon spectrum in which one can also place the condition described by Illum et al. [1988].

With regard to the audiological evaluation, auditory brain stem responses could not be elicited bilaterally. This result indicates bilateral sensory-neural hearing loss due to a lesion of the auditory periphery. Nevertheless, taking into account the CT findings, it was impossible to rule out the hypothesis of an abnormal electrogenesis of the response due to dysfunctions of the brainstem auditory pathway [Arslan et al., 1986]. Whether this latter problem is an incidental finding or is part of the syndrome remains unclear since very few reported cases have undergone an assessment of hearing. A systematic imaging (CT or MRI) and auditory evaluation may aid in clarifying the nature of these findings and their prognostic relevance.

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